Recreational and occupational field exposure to freshwater cyanobacteria – a review of anecdotal and case reports, epidemiological studies and the challenges for epidemiologic assessment

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Abstract

Cyanobacteria are common inhabitants of freshwater lakes and reservoirs throughout the world. Under favourable conditions, certain cyanobacteria can dominate the phytoplankton within a waterbody and form nuisance blooms. Case reports and anecdotal references dating from 1949 describe a range of illnesses associated with recreational exposure to cyanobacteria: hay fever-like symptoms, pruritic skin rashes and gastro-intestinal symptoms (the latter probably related to ingestion of water) are most frequently reported. Some papers give convincing descriptions of allergic responses to cyanobacteria; others describe more serious acute illnesses, with symptoms such as severe headache, pneumonia, fever, myalgia, vertigo and blistering in the mouth. A coroner in the United States recently found that a teenage boy died as a result of accidentally ingesting a neurotoxic cyanotoxin from a golf course pond; this is the first recorded human fatality attributed to recreational exposure to cyanobacteria. One of the main public health concerns with exposure to freshwater cyanobacteria relates to the understanding that some blooms produce toxins that specifically affect the liver or the central nervous system. The route of exposure for these toxins is oral, from accidental or deliberate ingestion of recreational water, and possibly by inhalation. Cyanobacterial lipopolysaccharides (LPS) are also reported to be putative cutaneous, gastrointestinal, respiratory and pyrogenic toxins.

This review introduces the topic of cyanobacteria in recreational waters with a brief discussion of the main cyanotoxins. A comprehensive review of anecdotal and case

reports of human illness attributed to recreational and occupational exposure to cyanobacteria follows, with discussion of some important papers. Epidemiological studies of recreational exposure to cyanobacteria are reviewed. Discussion of some water-related risk factors that may be important differential diagnoses for cyanobacteria-related illness concludes the review.

Introduction

Cyanobacteria are a diverse group of prokaryotes that occupy a broad range of ecological niches by virtue of their age, having first appeared some 2.5 billion years ago, and specialisation. All cyanobacteria are photoautotrophic organisms, yet many can grow heterotrophically, using light for energy and organic compounds as a carbon source [1]. The cyanobacteria are a remarkably widespread and successful group, colonising freshwater, marine and terrestrial ecosystems, including extreme habitats such as Antarctic lakes, salt works and hot springs [2]. Cyanobacteria are common inhabitants of freshwater lakes and reservoirs throughout the world. Under favourable conditions, certain cyanobacteria can dominate the phytoplankton within a waterbody and form nuisance blooms.

Cyanobacteria have come to the attention of public health workers because many freshwater and brackish species can produce a range of potent toxins. This observation was first reported over 120 years ago, when sheep, horses, dogs and pigs were seen to die

within hours of drinking from a lake affected by a bloom of the brackish-water cyanobacterium *Nodularia spumigena* [3]. Since then, many reports of livestock and wild animal deaths have appeared in the literature. Such reports have been collated and discussed by several authors [4-10]. Some reports are dramatic in terms of the number of animals affected or the rapid progression of illness and death, with mass deaths of thousands of animals [11], and large animals succumbing within minutes [12, 13]. Laboratory-based toxicological investigations have confirmed that freshwater and brackish cyanobacteria produce several categories of toxin that are (with one exception – the saxitoxins) unique to cyanobacteria. The topic of cyanobacterial toxins has been widely studied, and many excellent texts and reviews are available, e.g. [8, 10, 13-26]. Details of the principal cyanotoxin groups that are significant from the public health perspective of acute exposure and outcome are summarised in Table 1. Lipopolysaccharides, which are defining structural components of Gram-negative cell walls, are discussed in the accompanying review by Stewart *et al* [27]. Cyanobacteria are rich sources of bioactive compounds; structurally diverse metabolites with cytotoxic, tumour-promoting and enzyme-inhibiting properties are known and presumably many more await discovery. Some of these metabolites are discussed by Bickel *et al* [28] and Forchert *et al* [29].

A recent report has shown that *β*-*N*-methylamino-L-alanine (BMAA), a neurotoxic non-protein amino acid associated with an atypical motor neurone disease/Parkinsonism/Alzheimer's-like dementia complex, is produced by a wide variety of cyanobacteria [30]. BMAA is thought to be capable of binding to endogenous proteins,

in which form it may function as a "slow toxin", and may be implicated in the aetiology of other long-latency neurodegenerative diseases such as Alzheimer's disease [31]. The public health implications of this cyanobacteria-related neurotoxicity hypothesis have been further discussed [32].

Cyanobacteria poisoning of humans has occurred through known and suspected exposure to cyanotoxin-contaminated drinking water supplies [33] and reviewed in: [8, 9, 34]; confirmed and suspected exposure to contaminated dialysate by patients undergoing haemodialysis [35-39]; and through recreational and occupational contact. This review will concentrate on the latter exposures.

Rationale and search criteria

All references that could be found in the medical and scientific literature, including conference proceedings, which describe specific incidents involving human illness and exposure to freshwater cyanobacteria in recreational or in-field occupational settings are summarised in Table 2. The following citation sources were not examined for this exercise:

- Reports of cyanobacteria-associated illness from recreational exposures to marine or estuarine waters

- Publications written in languages other than English – with the exception of the Russian paper by Pashkevich [40], which we were opportunistically able to have translated
- Newspaper reports – with three exceptions: two reports that describe the first human fatality to be attributed to recreational contact with cyanobacteria [41, 42]. At the time this review was submitted, these were apparently the only published references to describe the events surrounding this tragedy, so were included here because of their importance. The cyanobacteria research community awaits publication of a comprehensive case report in the scientific or medical literature. Another news article supplements a cursory description of cyanobacteria-associated illnesses; both the news report and the scientific publication appear to describe the same incident, with more detail provided by the journalist [43, 44]. There are undoubtedly many more publications in the news media that report suspected cyanobacteria-related human and animal morbidity and mortality: for example Duggan [45] and Ruff [46] reported on cyanobacteria blooms in Nebraska lakes that were associated with two dog deaths and more than 40 complaints of acute eye, upper respiratory, gastrointestinal and skin symptoms.

Anecdotal and case reports presented in this review were identified by the following search strategy:

1. PubMed and Web of Science electronic databases were searched with the MeSH and textword string "(cyanobacter* AND disease outbreaks) OR (cyanobacter* AND

environmental exposure) OR (cyanobacter* AND recreation*) OR (cyanobacter* AND epidemiology)".

2. Titles and abstracts (when available electronically) were perused to determine suitability for inclusion.
3. Bibliographies of identified primary papers and related review articles were reviewed to search for references not identified by electronic sources.
4. Publications and other sources identified and forwarded by experts working in this field were included.

The most recent update of the aforementioned electronic searches, conducted in June 2005, gave 258 citations, of which 244 were English-language publications, and 14 were non-English-language papers. Of these 14 reports, four (3x reviews; 1x primary article) were identified from abstracts and/or article titles as worth perusing for the presence of information about health-related events associated with recreational exposure to cyanobacteria [47-50]. We were again able to opportunistically have two of these papers translated (the primary article, in Dutch, and a German review paper), but there were no previously unreported references in those papers to specific illness events that were attributed to contact with cyanobacteria [47, 48]. Therefore it does not appear that there is a significantly large body of unexplored literature written in languages other than English that could contribute to this review. We also corresponded with an author of a publication in Finnish that we were unable to have translated; this paper discussed cyanobacteria-related illness in saunas [51]. The findings of that work were presented at an international conference, from which an English-language abstract was published. The authors

reported that 18 subjects (38% of those questioned) were likely to have experienced cyanobacteria-related symptoms [52].

Recreational and in-field occupational exposure to cyanobacteria: anecdotal and case reports

Case reports and anecdotal references presented in Table 2 date from 1949 [53], and describe a range of illnesses associated with recreational exposure to cyanobacteria: hay fever-like symptoms, pruritic skin rashes and gastro-intestinal symptoms are most frequently reported. Some papers give convincing descriptions of allergic responses to cyanobacteria [53, 54]. Others describe more serious acute illnesses, with symptoms such as severe headache, pneumonia, fever, myalgia, vertigo and blistering in the mouth [6, 55-57]. The first and so far only description of a fatality attributed to recreational exposure to cyanotoxins appeared in news reports recently. A U.S. coroner concluded that a teenage boy died as a result of ingesting anatoxin-a-producing cyanobacteria from a golf course pond, although there was an unusual sequence of events preceding the death insofar as the time period between exposure and death (some 48 hours) does not square with the known mechanisms of toxicity of purified anatoxin-a, which initiates pathological signs in laboratory animals within minutes of dosing [41, 42]. Recent reports in the scientific literature also cast uncertainty on this finding, with suggestions that the preliminary mass spectrometric identification of anatoxin-a in these forensic samples may

not be reliable [58-60]. The cyanobacteria research community awaits a comprehensive case report on this matter.

The principal public health concerns regarding recreational exposures relate to the potential, presumably a now-realised potential if the aforementioned fatality is indeed attributable to cyanotoxin poisoning, for exposure to hazardous levels of cyanotoxins in untreated waters. Routes of exposure are through direct contact with skin and mucous membranes, via inhalation, and by ingestion, either accidental or deliberate.

Discussion of anecdotal and case reports

Some reports listed in Table 2 present scant information relevant to this topic, with little or no detail beyond location and the kind of illness reported [61, 62]. On the other end of the scale are examples of thorough, considered case reports, describing relevant medical history and diagnostic investigations [53, 54]. One reason for the dearth of detail may be that non-specific, mild and self-limiting illnesses do not merit much discussion, however, some references to more serious illnesses leave a great deal unanswered, for example the 12 year-old boy who reportedly lapsed into unconsciousness for a six-hour period, and developed pneumonia, myalgia and arthralgia [63]. It would have been very interesting to know whether or not this boy had any predisposing medical conditions (e.g. diabetes, epilepsy) that might have explained the loss of consciousness, whether any medical attention was sought, and, if so, the details of his disease progression.

The observation that repeated water contact in a particular lake preceded a skin eruption on a six year-old girl, while other bathers appeared unaffected, helped support a diagnosis of hypersensitivity in that case [54]. One of the few reports of mass effects, with 20-30 children suffering conjunctival and upper respiratory symptoms during a school aquatic event, is tempered by the observation that that number represented about 25% of those exposed [64]. So hypersensitivity reactions affecting a sub-set of allergy-prone children may also be an explanation for the latter outbreak, although this speculation – in the absence of any other reported investigations – is solely based on that estimate of 25% of those exposed experiencing symptoms.

Those reports that have indicated symptom onset time suggest that responses can be rapid, with some urticaria and hayfever-like symptoms commencing while subjects are still in the water [53, 64]. While a disparate range of signs and symptoms are listed, many reports describe a collective group of symptoms resembling immediate or Type-I hypersensitivity reactions. Immediate hypersensitivity reactions are commonly associated with atopy, which is the familial tendency to react to naturally occurring antigens, mostly proteins, through an IgE-mediated process. Atopy frequently manifests as a spectrum of diseases, e.g. seasonal rhinitis, conjunctivitis, asthma and urticaria. Different atopic illnesses often affect the same individual. A fundamental feature of Type-I hypersensitivity reactions is the rapid onset of symptoms – normally seconds to minutes – following exposure to antigens [65-69].

Some serious though apparently self-limiting gastro-intestinal illnesses have been reported after contact with cyanobacteria in recreational waters, presumably through ingestion of affected water. Dillenberg & Dehnel [55] describe how an adult male inadvertently swallowed lake water affected by a bloom of *Microcystis* sp. and *Anabaena circinalis*. After some three hours he developed cramping abdominal pain and nausea, which progressed to painful diarrhoea followed by a fever of 38.9^0C, severe headache, lassitude, myalgia and arthralgia. Such illnesses are worrying, considering the two boys that were sickened – one of whom subsequently died – after possible exposure to cyanobacteria in a golf course pond suffered acute and severe gastro-intestinal illnesses [41].

Occupational exposures were included in this review, although some caution should be exercised when comparing occupational and recreational exposures. Waters that are obviously discoloured or visibly affected by cyanobacteria scums may be of interest to aquatic field workers who are keen and/or obliged to collect samples. The two incidents involving British soldiers and sea cadets conducting canoe capsizing activities, presumably under orders from their supervising officers, occurred in waters that were reportedly subject to a "heavy bloom of *Microcystis* spp" [70] and a "scum of *Oscillatoria*…" [23]. Waters that are obviously suffering a loss of visual amenity may be shunned by many recreational users, although avoidance behaviour in such circumstances cannot be taken for granted [71].

The other reports that are of particular interest are those grouped under "cold & flu-like symptoms". Several publications describe individuals presenting with a flu-like illness, with signs and symptoms including fever, headache, lassitude, arthralgia, myalgia, sore throat, cough, diarrhoea and vomiting. A proposed explanation for this constellation of symptoms is that of a coordinated, cytokine-mediated, innate immune response. Fever and malaise are events that are directed by endogenous mediators; for further discussion see [71]. This spectrum of signs and symptoms also mimics those reported in volunteer studies of intravenous Gram-negative bacterial LPS injection [72-75]. Mammalian responses to LPS are mediated by inflammatory cytokines (see accompanying review by Stewart *et al* [27]). The early signs and symptoms of influenza infection (fever, myalgia, fatigue, drowsiness, rhinorrhoea, sore throat, headache) are mediated by pro-inflammatory cytokines, particularly IFN-α and IL-6 [76-79]. Flu-like reactions to immunostimulant drugs are sometimes referred to as "acute cytokine syndromes" [80], and the flu-like syndrome of fever, rigors, tachycardia, malaise, headache, arthralgia and myalgia that accompanies interferon pharmacotherapy is thought to be due to the release of eicosanoids, IL-1 and TNF-α [81].

Epidemiology of recreational exposure to cyanobacteria

Six epidemiological studies of recreational exposure to cyanobacteria were identified with the search strategy discussed previously: three analytical cross-sectional studies from the U.K. using similar survey instruments [82-84], a small case-control study from

Australia [85], and two larger prospective cohort studies, also from Australia [86, 87]. Table 3 lists the pertinent findings of these studies, which are discussed in detail below.

The three cross-sectional studies were conducted by Philipp and co-workers [82-84]. Questionnaires were distributed to recreational users of six inland waterbodies, five of which experienced cyanobacteria blooms during 1990. The questionnaires elicited information on exposure to study waters and the presence of specific symptoms in a defined period prior to receiving the form. This period ranged from 14 days [83] to four weeks [84]. One questionnaire asked about exposure to the study water on a weekend when a bloom occurred some 2½ weeks previously [82]. Recreational interest groups were used to target likely users of the waterbodies; questionnaires were mailed to members of sailing and angling clubs. Site authorities distributed questionnaires at one study lake [84]. The results of these three studies were similar: mostly minor morbidity was reported, with similar disease patterns across sites.

The theoretical advantages of this study type are that it is reasonably cost-effective, and in this context – recreational exposure to cyanobacteria – it can be conducted opportunistically to take advantage of any sudden-onset cyanobacteria blooms. Disadvantages relate to the difficulty in establishing that exposure occurred before the outcome [88, 89]. The studies conducted by Philipp and his team [82-84] were examples of analytical cross-sectional studies, in that unexposed individuals served as controls for statistical comparison of illness reporting.

A case-control study of illness rates was conducted after an extensive *Anabaena circinalis*-dominant bloom along South Australia's Murray River in the summer of 1991-1992 [85]. Patients presenting with gastro-intestinal (G-I) or dermatological complaints comprised the case group; the patient presenting after each case was identified served as the control group. Exposure was determined by identifying each subject's principal source of water for drinking, domestic use (bathing, dishwashing) and recreation during the week prior to consultation. Recreational exposure was categorised as no contact, direct exposure to river water, or other exposure, e.g. farm dams or treated water in swimming pools. The study found a significantly increased risk of G-I symptoms for those drinking chlorinated river water, and an increased risk of G-I and cutaneous symptoms in those using untreated river water for domestic purposes. The study found a statistically non-significant increase in the relative odds of developing G-I or skin symptoms amongst those with recreational exposure to river water, but that risk was lower than for those exposed to other sources of recreational water (tank, farm dam or another location). The number of subjects was small for the recreational exposure component of the study, with only some 50 subjects (16% of the study group) reporting any recreational exposure during the study period [85].

The advantages of a case-control design for investigating recreational exposure to cyanobacteria are that studies can be conducted opportunistically in response to the development of cyanobacteria blooms, and they are very useful for investigating infrequent outcomes. The study of El Saadi *et al* [85] has another advantage over other epidemiological studies into recreational exposure to cyanobacteria in that medical

practitioners ascertained outcome data, as opposed to self-reporting of symptoms. General disadvantages of the case-control design principally relate to the problem of recall bias, where individuals with the disease of interest tend to overestimate relevant past exposures [88, 89]. Because the outcome has already occurred when exposure is measured, people with disease may systematically overestimate (or underestimate) their exposure compared to disease-free controls, leading to falsely elevated (or reduced) measures of risk associated with exposure. Another major issue with case-control studies is the difficulty of identifying an appropriate control group – i.e. people who would have been identified as cases if they had the disease of interest.

Recall bias may not be so much of a problem for investigating acute illnesses following recreational exposure to cyanobacteria, where a fairly short time lag between exposure and symptom onset can be anticipated, especially if recreational exposure is determined by a yes/no response. The main problem with a case-control study in this context will be in actually identifying cases. A case-control design would not be suitable for investigating outcomes from exposure to a cyanobacteria bloom in a lake adjacent to a city, as most recreational users who do develop symptoms would presumably seek medical attention after they return home, i.e. from one of a large number of medical practitioners. El Saadi *et al* [85] alluded to the difficulty of gaining the cooperation of medical practitioners, as they approached practices in 11 towns along the Murray River, yet those in three towns presumably refused to participate in their study. The diffuse spread of cases from point sources of exposure (a cyanobacteria-affected waterbody) across a large town or city would make a case-control study practically unworkable. A

case-control study would also be unsuitable for recruiting subjects who did not seek medical attention for symptoms occurring after exposure. However, a well-designed case-control study would be valuable if geographical location is a primary consideration. This would require enlisting the cooperation of medical practitioners in small townships near to cyanobacteria-affected recreational waters that are sufficiently remote from larger urban centres to allow recruitment of local residents and tourists who will camp nearby.

The studies by Pilotto *et al* [86] and Stewart *et al* [87] were prospective cohort studies. Pilotto *et al* [86] recruited individuals at five recreational waterbodies in three Australian states. Cyanobacteria blooms were anticipated at these sites, based on occurrences in previous years. Individuals were approached and invited to participate in the study. Participants completed a face-to-face interview to determine health status and recreational water activities; two telephone follow-up interviews were conducted at two and seven days following the day of recruitment into the study. Individuals who did not have water contact on the recruitment day served as the control group. No significant differences in symptom occurrence were reported at the 2nd day follow-up, but the authors concluded there was a significant increase in symptoms at 7 days, after excluding subjects with symptoms or previous recent recreational water exposure. The cohort size from which these significant results were drawn was rather small, with 93 exposed subjects, and 43 unexposed controls. Pilotto *et al* [86] interpreted the increased symptom reporting at 7 days but not 2 days following exposure as possibly due to delayed allergic responses, although so-called “late phase” allergic and asthmatic responses tend to occur some 4-24 hours after allergen exposure [65, 90, 91].

Stewart *et al* [87] also conducted a cohort study of recreational exposure to cyanobacteria. 1,331 subjects were recruited from 19 recreational waterbodies in eastern Australia and central and northeast Florida; subjects completed a self-administered questionnaire to determine recreational activity, recent illness and history of any relevant chronic diseases such as asthma, hay fever and eczema. A single follow-up telephone interview was conducted after three days post-exposure. Reference subjects were recruited at recreational waters unaffected by cyanobacteria; exposure categories (low, intermediate, high) were allocated to study subjects on the basis of cyanobacteria levels measured in study water samples collected on the day they were recruited into the study. Statistically significant increased reporting of respiratory symptoms and a pooled "any symptom" category occurred amongst subjects exposed to high levels of cyanobacteria, although symptoms were predominantly rated as mild by study subjects. A similar but non-significant relationship was also seen for reporting of skin, ear and fever symptom groups.

The studies of Pilotto *et al* [86] and Stewart *et al* [87] are both examples of a prospective cohort design, where study subjects have their exposure status determined, and are then followed forward in time to observe the development of disease. For these investigations into recreational exposure to cyanobacteria, exposure status was determined by collecting water samples on the day subjects were recruited into the study; cyanobacteria were identified and enumerated and the resultant cell counts or biomass estimates formed the basis of exposure at any given site on a particular day. One of the problems with this

approach is that cyanobacterial blooms are dynamic and can change rapidly. Unless the presence of significant cyanobacterial biomass can be predicted with some degree of certainty, a prospective cohort design can result in wasted effort if the water samples reveal lower than anticipated levels of cyanobacteria. This problem undoubtedly occurred in some instances during the study conducted by Stewart *et al* [87]. One possible approach to dealing with this would be to conduct a historical cohort study, where a cohort of subjects is identified after some have experienced the outcome of interest and relevant exposure information is obtained from historical records (i.e. as in a prospective cohort study the exposure information was recorded *before* any outcomes occurred).

Whether a cohort study is conducted prospectively or retrospectively, the basic study design is identical – exposed and unexposed groups are compared with respect to disease outcome [89]. General advantages of a cohort design are the ability to determine disease onset (the exposure precedes the disease), and the study of exposures in natural settings [88]. General disadvantages relate to confounding, which refers to differences in the distribution of risk factors other than the exposure of interest between exposed and unexposed groups. Cohort studies can be expensive and resource intensive [88].

Further discussion of some common epidemiological study designs that may be useful for investigating the topic of recreational exposure to aquatic cyanobacteria, with particular emphasis on the relative advantages and disadvantages of experimental epidemiology (randomised trials) is presented by Stewart [71].

Cyanobacteria and water-related disease: some complicating factors

Other explanations for disease need to be considered by both clinicians and epidemiologists in their respective endeavours. Epidemiological studies usually aim to identify and adjust for confounding variables such as smoking and age of study participants. The following sections will discuss some freshwater-related risk factors, mostly microbial, that may confound epidemiological studies and complicate clinical diagnoses of cyanobacteria-related illness linked to recreational exposures. The final section of this review will discuss the possibility of misdiagnosis from the opposite direction: a water-borne disease outbreak in Finland that was subject to epidemiological scrutiny, but cyanobacterial exotoxin contamination of reticulated supplies was apparently not considered at the time.

Freshwater-related dermatoses

- **Avian cercariae:** avian cercariae are schistosome larvae for which humans are an accidental host. Pruritus and macules are the initial signs and symptoms; sometimes a diffuse erythema and urticaria can develop and last for several hours [92-95]. Fever, nausea and vomiting can also accompany severely affected cases [93, 96]. The clinical presentation of cercarial dermatitis can be difficult to delineate from the picture of cyanobacterial dermatitis.

- **Gram-negative bacteria:** *Aeromonas hydrophila* and *Chromobacterium violaceum* are abundant in freshwater habitats. Both usually cause infection through a pre-existing skin wound, though the clinical picture in each case is not reminiscent of any of the reports listed in Table 2. *A. hydrophila* causes cellulitis and a purulent discharge; aspiration of water can cause pneumonia and septicaemia. *C. violaceum* infections present with various cutaneous signs that are secondary to systemic disease, including sepsis [97]. *Vibrio vulnificus* has reportedly caused soft tissue infection after contact in brackish inland waters, though most cases are associated with estuarine contact [98]. *Pseudomonas aeruginosa* is widely-distributed in natural and artificial aquatic environments. Cutaneous infection presents as an erythematous or urticarial rash some 18-24 hours after water contact and progresses to a follicular dermatitis. Fever and pruritus are uncommon. Most reports of pseudomonal dermatitis are related to spa pool or hot-tub exposures [98, 99]. *P. aeruginosa* in recreational waters is a common cause of otitis externa, presenting as a purulent discharge [98]. Diagnostic criteria include culturing the organism from skin or ear swabs; the incubation period would also help to distinguish *P. aeruginosa* infection from cyanobacteria-related dermatoses.

- **Non-allergic urticaria:** physical stimuli such as heat, cold and exercise can induce itching and hives in susceptible individuals [95, 100].

Gastro-intestinal illness

- **Shigellosis:** Shigella outbreaks are the most commonly reported cause of disease associated with untreated inland recreational water in the USA, with 16 events affecting almost 1,300 people between 1985 and 1994 [98]. The incubation period is typically 2-3 days, with an upper limit of about 7 days. Illness severity is strain-dependent, with most *S. sonnei* infections being mild and self-limiting, and *S. dysenteriae* type 1 associated with severe diarrhoea which may progress to a life-threatening illness [98].

- ***Escherichia coli*:** *E. coli* are markers of faecal pollution in recreational waters. Disease outbreaks traced to enterohaemorrhagic *E. coli* 0157 have been reported from recreational water exposures [98, 101].

- **Norwalk-like viruses:** Various transmission routes, including recreational water outbreaks have been documented [101].

Other microbial pathogens

- ***Naegleria fowleri*:** *N. fowleri* is a free-living thermotolerant amoeba found in warm or thermally polluted waters. It is the causative organism of primary

amoebic meningoencephalitis, a fulminating, typically fatal illness. The entry route is via the nasal mucosa; fit, immunocompetent children and young adults with a recent history of freshwater recreational activity are those most commonly affected. The causative organism and diagnosis are usually confirmed at autopsy. Several reviews are available, e.g. [102-109].

- **Viruses:** Pharyngo-conjunctival fever outbreaks associated with non-enteric adenoviruses in recreational waters have been reported [101].

- **Legionella:** *Legionella* infections have been associated with recreational water contact [101].

Possible under-diagnosis of cyanobacteria-related illness

The examples given above highlight some of the differential diagnoses that need to be worked through when considering possible cases of cyanobacteria-related illness from recreational exposures. Competent history-taking and diagnostic microbiology support will correctly diagnose many such cases. Competent history-taking and clinical diagnostic support also operated in several of the case reports listed in Table 2, with the early dermatological testing and microscopic examination of stool and vomitus samples lending strong support to the suspicion of cyanobacteria-related morbidity.

Misdiagnosis of cyanobacteria-related disease may occur in both directions. In 1978, nearly half the population of an industrial town in Finland were affected by a flu-like illness, with symptoms of fever, fatigue, cough, dyspnoea and myalgia. Symptoms occurred some 3-6 hours after taking a bath, shower or sauna and persisted for 8-16 hours. The outbreak lasted for some four months. This epidemic was investigated on several fronts, and provocation testing demonstrated an obvious link to the reticulated water supply. Tap water was cultured in a range of organic media for fungal and bacterial pathogens. No definitive pathogen was identified to explain the epidemic, yet in three published reports the authors describe how the shallow lake that was the town water source had taken on a distinct opaque blue-green appearance, had a musty smell, and the sand filtration system was covered by a mat of cyanobacteria. This change occurred in the same month (August, i.e. late summer) that the epidemic began. Analysis of crude lake water in the third month after the onset of the epidemic showed high coliform counts, *Aspergillus fumigatus* and unspecified blue-green algae. Investigations centred on identifying antibodies to mesophilic actinomycetes, which the authors [110] note were not pathogenic, whereas aquatic cyanobacteria were known at the time to be toxic. The health workers investigating the outbreak apparently did not consider the possibility of a cyanobacterial exotoxin breakthrough into the reticulated supply [110-114]. The epidemiological report of Aro *et al* [111] came closest to suggesting that cyanobacteria may have been involved, suggesting that "towards the end of summer….the microorganisms in the lake multiply rapidly and produce some toxic substance or allergen", and reported that cyanobacterial endotoxin concentration in lake and tap water was high. This incident appears to have been retrospectively attributed to the presence of

cyanobacterial endotoxins in the reticulated supply [115]. A similar outbreak occurred almost three years earlier in a Swedish town, though with a much smaller proportion of cases identified. Cyanobacteria were known to affect the town's raw water supply, and the investigators did consider the possibility that cyanotoxins may have been responsible for the outbreak [116], though the analytical technique used by investigators at the time – gas chromatography – would have failed to detect the presence of cyanobacterial exotoxins in the post-treatment water supply. While no conclusions can be made about events that occurred over 25 years ago, from the descriptions of the outbreaks and the raw water supplies, most cyanobacterial toxicologists would rate cyanotoxin exposure with a high index of suspicion.

A similar outbreak occurred more recently in Homa Bay, Kenya, in 1998. Apparently associated with a mass development of cyanobacteria in Lake Victoria, an epidemic of fever, malaise, dizziness and upper respiratory symptoms was related to hot water bathing. Symptoms lasted 12-24 hours, and returned when a shower or bath was taken again. This outbreak was reported in a conference abstract; the authors suggested cyanobacterial endotoxins were responsible, though it is not stated whether any investigation of cyanobacterial exotoxins was conducted [117].

Conclusions

The true incidence of acute cyanobacteria-associated illness from recreational exposure is unknown, as many outcomes are likely to be mild and self-limiting, so medical attention is not sought. With a long-standing knowledge gap amongst primary healthcare providers, non-specific signs and symptoms caused by cyanobacterial products are likely to be under-diagnosed [8]. Codd [118] stated:

> *"Evidence linking human illnesses with cyanobacterial cells and toxins is open to criticism because of shortfalls in early detailed case definitions, because diagnoses were made by exclusion, and because identification and quantification of cyanobacterial toxins in health incidents have, until recently, been lacking."*

The collation of anecdotal and case reports of illness associated with recreational exposure to cyanobacteria in Table 2 will hopefully highlight some of the knowledge gaps. Particular attention should be given to determining the onset and duration of individual symptoms in future case reporting, as well as detailing the presence or absence of any predisposing medical conditions.

A recent initiative of UNESCO's International Hydrology Programme has been to establish CyanoNet, which is a "Global network for the hazard management of cyanobacterial blooms and toxins in water resources". The CyanoNet website will carry information on various associated topics, including "Reported incidents of adverse health effects including case studies" and "Surveys and epidemiological studies investigating associations between cyanobacterial populations, cyanotoxins and health" [119].

The most important advances in understanding the health impacts of cyanobacteria have come from the discipline of toxicology. The major toxins have been extensively studied and characterised, and while there is still much to be discovered in the field of cyanobacterial toxicology, significant advances in the future will be made at the interface of toxicology and epidemiology. Molecular epidemiology techniques using yet-to-be discovered biomarkers of exposure, susceptibility and outcome will refine knowledge of the risks associated with various acute and chronic exposures to cyanotoxins. The collaborative skills that epidemiologists and toxicologists can bring to this endeavour were visualised with a mildly jaundiced eye by Paddle [120], whose chapter on epidemiology for toxicologists is an excellent general primer:

> *"The total evidence about the risk to humans…will consist of the toxicologist's precise, experimental data about the wrong species at the wrong exposure, and the epidemiologist's imprecise, observational data about the right species at the right exposure."*

In conclusion, anecdotal and case reports of variable reliability have suggested a range of symptoms are associated with exposure to cyanobacteria in recreational or occupational settings. Some reports of cutaneous reactions are strongly suggestive of allergic reactions, and symptoms such as rhinitis, conjunctivitis, asthma and urticaria also hint at immediate hypersensitivity responses. Flu-like illnesses involving a constellation of symptoms including fever, malaise, myalgia, arthralgia, severe headache, cough and sore throat are,

in our opinion, explained by a cascade action of pro-inflammatory cytokines. If correct, this implies that some cyanobacterial products possess ligands that signal innate immune responses, and such responses may need to be considered in terms of their potential to direct pathological changes in the liver and other organ systems.

The epidemiology of recreational exposure to cyanobacteria is incomplete at present. All common epidemiological approaches have their own inherent advantages and disadvantages; identification of biomarkers for exposure, susceptibility and outcome in the future should lead to a significantly improved perception of the risks of bathing in cyanobacteria-affected waters.

Abbreviations

BMAA	*β*-*N*-methylamino-L-alanine
G-I	gastro-intestinal
IFN	interferon
IgE	immunoglobulin-E
IL	interleukin
i.p.	intra-peritoneal
LPS	lipopolysaccharide(s)
TNF	tumour necrosis-factor

Competing interests

The authors declare that they have no competing interests.

Author contributions

IS conducted the review; PMW, PJS and GRS supervised the work and contributed to redrafting the paper. All authors read and endorsed the final manuscript.

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Table 1. Cyanotoxins with public health significance from acute exposures

Toxin or toxin group	Classification by principal target organ systems	Toxin-producing genera	LD_{50} (i.p. mouse)	References
Microcystins	Hepatotoxins	*Anabaena, Anabaenopsis, Aphanocapsa, Arthrospira, Hapalosiphon, Microcystis, Nostoc, Oscillatoria, Planktothrix, Snowella, Woronichinia*	25->1000 µg/kg	[10, 19, 26, 121-124]
Nodularins	Hepatotoxins	*Nodularia*	30-60 µg/kg	[8, 26, 125]
Anatoxin-a, homoanatoxin-a	Neurotoxins	*Anabaena, Aphanizomenon, Arthrospira, Cylindrospermum, Microcystis, Oscillatoria, Phormidium, Planktothrix, Raphidiopsis*	200-375µg/kg	[8, 10, 18, 26, 126-131]
Anatoxin-a(s)	Neurotoxin	*Anabaena*	20-40µg/kg	[8, 26, 128]
Saxitoxins	Neurotoxins	*Anabaena, Aphanizomenon, Cylindrospermopsis, Lyngbya, Planktothrix*	10-30µg/kg	[26, 123, 128, 132-136]
Cylindrospermopsin	General cytotoxin (multiple organ systems affected, incl. liver, kidney, gastrointestinal tract, heart, spleen, thymus, skin)	*Anabaena, Aphanizomenon, Cylindrospermopsis, Raphidiopsis, Umezakia*	2.1mg/kg (24 hours) 200µg/kg (5-6 days)	[8, 10, 17, 128, 137-141]
Aplysiatoxin, debromoaplysiatoxin	Dermal toxins; possible gastro-intestinal inflammatory toxin	*Lyngbya*	107-117 µg/kg	[142-147]
Lyngbyatoxin A	Possible gastro-intestinal inflammatory toxin	*Lyngbya*	250 µg/kg (?LD_{100})	[148]

TABLE 2. Reports of human morbidity and mortality attributed to recreational exposure to freshwater cyanobacteria

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Hayfever-like symptoms (conjunctivitis, rhinitis, sneezing)														
1934	Late summer	Muskego Lake, Waukesha County, WI, USA	Report of single subject, male	N/S	57	Swimming	Itching of eyes, nasal congestion	"weedy lake"	3 hours	<48 hours		History of frequent sinus infections		[53]
1935	Late summer	Muskego Lake, WI, USA	Same subject	N/S		Swimming	Same symptoms, + mild asthma		As above	As above				[53]
1936-1946	Late summer	North Lake, Waukesha County, WI, USA	Same subject	N/S		Swimming	Nasal discharge and congestion, conjunctivitis, mild asthma	Oscillatoreaceae (sample taken in late summer, 1944)	N/S	N/S	Surface scum extracts gave immediate skin reactions. Cutaneous injection of 0.03mL of 1:1,000 dilution resulted in mild asthma within 20 mins. Control subjects did not react to scum extracts		Subject swam in North Lake during summer months over the ten-year period, without incident until mid-August each year, when swimming was followed by symptom onset. Desensitisation injections over 4 years were successful	[53]
1979	Late summer	Lake Wallenpaupack, PA, USA	5 (family group)	N/S	N/S (parents + son + daughter + friend)	Swimming	"Severe" hayfever-like symptoms (sneezing, nasal discharge, eye irritation): 3/5 earache: 2/5	N/S. Lake developed a distinct green colour several days prior to incident. Three weeks later: heavy bloom of *Anabaena*	Hayfever symptoms: during exposure; earache: several hours after exposure	N/S		N/S		[64]
1979	Late summer	Lake Wallenpaupack, PA, USA	20-30	60-90 (those affected comprised approx 25% of aquatic event participants)	N/S (high school students)	Participating in school aquatic event	Eye irritation, sore throat, earache, sneezing, nasal discharge, swollen lips	N/S. see above	During exposure or within 2-3 hours	Within 2-3 days *Subsequent exposure reportedly caused re-occurrence of symptoms		N/S	Affected individuals were members of a high school summer aquatic program. The event was cancelled because of these illnesses	[64]
N/S	N/S	N/S	Single male	N/S	N/S (adult)	Swimming	Hayfever-like symptoms	Bloom of *Microcystis*	N/S	N/S		N/S		[149]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Cutaneous symptoms														
1949-1952	Summer	Lake Carey, PA, USA	Report of single subject, female	Reported skin rash "never appeared in other bathers swimming in the same water"	6 (condition first seen at age 3 years)	Swimming	Seasonal erythematous papulo-vesicular rash, occasionally progressing to oozing and crusting. Rash limited to face, neck, shoulders, upper chest and extremities; rash never seen on areas covered by swimsuit	*Anabaena*	1-2 hours	< 2 weeks (if no further contact with lake water)	Skin patch testing: strong positives to *Anabaena* filtered from lake water, chloroform extract of same, and phycocyanin extract	None (apart from reported condition)	Rash never seen after swimming in artificial pools or ocean. Only seen after water exposure at Lake Carey, and once after bathing in a Canadian lake	[54]
Late 1940s & mid 1950s	Late summer	Lake Ringsjön, Scania, Sweden	"several" members of a family	N/S	N/S ("young girl" + siblings)	Swimming	Pruritic skin rashes	*Gloeotrichia echinulata*	N/S	N/S				[150, 151]
1977	Summer	Mingechaur Reservoir, Azerbaijan	7	13	N/S	Swimming	Slightly raised, erythematous spots, 2-6mm diameter; seen on skin bordering and outside swimsuit	Benthic *Lyngbya kützingii*; also "planktonic blue-green algae colouring the water"	2nd day after swimming	10-12 days				[40]
1985	N/S	UK	N/S	N/S	N/S	Sail-boarding	Skin rashes	N/S ("toxic blooms")	N/S	N/S		N/S		[61]
1989	N/S	Japan (lake)	1	N/S	N/S (adult)	Collecting algal scum *	Rashes	*M. aeruginosa* containing microcystins	N/S	N/S		N/S		[61]
1989	Late summer – early autumn	Bewl Water, Kent, UK	1	N/S	N/S	Fishing	'blotchy' skin on face and hands after handling water on three separate occasions	*Microcystis* sp	Within two hours	Several days		N/S		[61]
1989	N/S	NRA South West Region, UK	N/S ("some NRA staff")	N/S	N/S (adults)	Sampling water *	Tingling sensations on hands	**"Potentially toxic cyanobacteria species"**	N/S	N/S		N/S		[61]
1989	Early-mid autumn	Welton Water, Yorks, UK	N/S	N/S	N/S	N/S ("water users")	Rashes	*Anabaena* sp	N/S	N/S		N/S		[61]
1991	Late spring – early summer	Darling-Barwon river system, NSW, Australia	N/S	N/S	N/S (adults)	Sampling water*	Skin irritation	*Anabaena* spp	N/S	N/S		N/S		[152]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Cutaneous symptoms														
2003	Summer	Lake Salajärvi	1	N/S	N/S	Swimming	Rash	*Anabaena lemmermannii* (dominant) + minor proportions of *M. aeruginosa* and *M. flos-aquae*. Saxitoxin, microcystins and anatoxin-a products present in water samples	N/S	N/S		N/S		[153]
2003	N/S	Lake Sompanen, Finland	1	N/S	7 yo male	N/S	"extensive" generalised rash	Cyanobacteria visible in water; saxitoxin found in water samples in 2002 & 2004	N/S	N/S		N/S		[153]
Gastro-intestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain)														
1959	Summer	One of Katepwa Lakes, SK, Canada	Report of single subject, male	N/S	N/S (adult)	Swimming	Headache, nausea, G-I upset	N/S	During night after swimming	<48 hours.	Stool sample showed "many tiny greenish spheres which resembled in size and morphology the cells of *Microcystis*". Stool specimen negative for *Salmonella* and *Entamoeba*	N/S	Subject sought medical advice for gastroenteritis, admitted to hospital, given oral chloramphenicol. Recovery within 24 hours of admission	[55]
1959	Summer	Long Lake, SK, Canada	10	N/S	N/S (children)	Swimming	Diarrhoea, vomiting	N/S. Subjects swam in "algae-covered lake water". Dried *Microcystis* and *Anabaena* scum found later on shore	N/S. Reported to local medical officer with illness on the day after exposure	N/S	Stool specimen from one child contained cells resembling *Anabaena* "in great numbers"		Local farmer reported that two cows died after drinking from the lake 12-16 hours previously, during an algal bloom. A third sick cow recovered after receiving penicillin injections	[55]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Gastro-intestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain)														
N/S	N/S	N/S (lake)	Single subject, male	N/S	4	Fell into lake, swallowed water #	Abdominal pain, nausea, vomiting, diarrhoea, wooziness, headache, thirst	N/S	Day of exposure: G-I symptoms; next day: wooziness, headache, thirst	N/S	*Aphanizomenon* found in stool and vomitus specimens	N/S		[63]
1961	N/S	N/S	4	N/S	N/S (students)	Swimming	Headache, malaise, diarrhoea	Heavy growth of *Microcystis* and *Anabaena*	N/S	N/S		N/S		[63]
1989	Early autumn	Rutland Water, Leics, UK	N/S	N/S	2 & 3 year-olds	Playing at edge of scum	Vomiting & diarrhoea	*M. aeruginosa*	N/S	N/S	Microcystin-LR found to be principal cyanobacterial toxin present	N/S	20 sheep and 15 dogs died over approx 3 weeks in late summer – early spring after contact with bloom scum	[6]
1990	N/S	Unnamed lake, Tiel, The Netherlands	N/S	N/S	N/S	Swimming	"G-I complaints"	*Anabaena flos-aquae*	N/S	N/S	Water quality parameters and food-borne pathogen testing negative	N/S	Mouse bioassay and HPLC-UV confirmed presence of anatoxin-a	[154]
2003	Summer	Lake Iso-Kukkanen, Finland	1	N/S	10 yo male	Swimming	Abdominal pains	*A. lemmermannii* sole or dominant cyanobacterium. Saxitoxin measured at 13-270 µg/L (depending on methods). Low levels of microcystins found. Anatoxin-a and degradation products reported	N/S	Several hours		N/S		[153]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Progression to fatal illness														
2002	Mid-summer	Golf course pond, Milwaukee, WI, USA	5	0	17 yo male and 4 friends	"splashing and diving". Two most severely affected boys had their heads under water for varying periods of time #	17-year-old developed nausea, vomiting, progressed to "shock" and "seizure", acute heart failure; death ensued approx. 48 hours after exposure. One teenager who also apparently ingested water developed severe diarrhoea and abdominal pain. The other three youths developed "minor symptoms"	Presumably *A. flos-aquae* containing anatoxin-a, determined from blood and stool samples of the boy that died and the other severely affected youth	N/S	N/S	Analysis of "tissue, blood and other fluid samples" from the two severely affected teenagers. Anatoxin-a found in unspecified sample/s. Autopsy showed "acute heart damage" but no evidence of meningitis or encephalitis. Analyses for pesticides, parasites and other pathogens negative	N/S	The unusual feature of this case is the length of time – 48 hours – that ensued between exposure and ingestion of contaminated water and subsequent death. Uncertainty exists regarding the identification of anatoxin-a in tissue samples	[41, 42, 58-60]
Cold & flu-like symptoms (incl. fever, headache, myalgia, arthralgia, sore throat, respiratory and gastro-intestinal)														
1959	Summer	Echo Lake, SK, Canada	Report of single subject, male	N/S	N/S (adult)	Intending to swim – fell into lake, swallowed an estimated half-pint of water #	Abdominal cramps and pain, nausea, vomiting, painful diarrhoea, fever, severe headache, weakness, pain in limb muscles and joints. Stools and vomitus were slimy and green	N/S. Lake had a visible bloom on day of exposure. *Microcystis* and *Anabaena* bloom 35 days prior to exposure	3 hours: abdominal pain, nausea, vomiting 5 hours: diarrhoea; next morning: fever, headache, myalgia, weakness	Recovering when questioned on 2nd day after exposure	Stool specimen showed "innumerable spheres of *Microcystis* and 2-3 well-preserved curved chains of *A. circinalis* per high-power field"	N/S	During bloom 35 days prior to exposure, an unknown number of dogs and geese died after swimming in the lake. Other dogs sickened after drinking lake water. Also fish kills	[55]
N/S	N/S	N/S (swimming hole)	Single subject, male	N/S	12	Swimming	Fever, loss of consciousness for six hours, dyspnoea, pneumonia, myalgia, arthralgia	Abundant *M. aeruginosa*	N/S (onset reported as sudden, with subsequent myalgia and arthralgia)	N/S	Stool sample: *Aeromonas* (Gram-negative bacteria), *Spirogyra* and *Mougeotia* (both green algae)	N/S		[63]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Cold & flu-like symptoms (incl. fever, headache, myalgia, arthralgia, sore throat, respiratory and gastro-intestinal)														
1979	Late summer	Lake Wallenpaupack, PA, USA	15	N/S	N/S	Swimming	Vomiting, nausea, diarrhoea, eye irritation, sore throat, fever, earache	N/S. See above.	Symptoms occurred "a short time after contact with lake water"	G-I symptoms: 24-48 hours		N/S	Affected individuals all holidaying in rental cottages. Well water to cottages free of bacterial contamination	[64]
1979	Late summer	Arrowhead Lake, PA, USA	Single female	N/S	N/S ("young girl")	Swimming #	Chills, sore throat, fever, nausea, diarrhoea	N/S	"within several hours"	Approx. 3 days		N/S		[64]
1989	Early autumn	Rudyard Lake, Staffs, UK	2	N/S	16	Swimming and canoeing exercises, the latter involving 360^0 rolls * #	Malaise, sore throat, circum-oral blistering, left-sided pleuritic pain, dry cough, vomiting, central abdominal pain, diarrhoea, fever	*M. aeruginosa*	Day after exposure	<2 weeks	Microcystin-LR found to be principal cyanobacterial toxin present	N/S	Both were hospitalised, having developed left lower-lobe pneumonia accompanied by thrombocytopenia	[23, 57, 70, 155, 156]
1989	Early autumn	Rudyard Lake, Staffs, UK	8	N/S	N/S (soldiers)	As above * #	Sore throat, headache, abdominal pain, dry cough, diarrhoea, vomiting, blistered mouth	*M. aeruginosa*	N/S	N/S	See above	N/S	All subjects were soldiers who had partaken in canoeing exercises, subsequently admitted to barracks medical centre	[23, 57, 70, 155, 156]
1992	Mid-spring	Darling River, Wilcannia, NSW, Australia	2	N/S	N/S - teenagers	Swimming	Gastroenteritis and myalgia	*Anabaena* sp	N/S	Symptoms resolved after 48 hrs	One subject required admission to hospital.	N/S	Some Wilcannia residents reported itchy skin rashes after showering, even after carbon filtration of the town water supply	[157]
N/S	N/S	Unnamed reservoir, UK	Single subject, male	N/S	39	Windsurfing	Fever, nausea, vomiting	N/S, but microcystin isolated from reservoir; several sheep and dogs died	N/S "shortly after windsurfing trip"	N/S	Liver function tests, liver biopsy	No significant past history, no medications	Mild hepatic dysfunction investigated six weeks after exposure	[158]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Mixed symptoms														
1945	Late summer	Lake Keesus, Waukesha County, WI, USA	Report of single subject, female	N/S	39	Swimming	Gross eyelid oedema, nasal congestion, generalised urticarial rash	N/S	"while swimming"	N/S	Skin test with Oscillatoreaceae extract (0.03mL of 1:10,000 dilution) resulted in immediate and severe local reaction treated by local injection of adrenaline	Long-standing history of autumn hay-fever and seasonal asthma	Oscillatoreaceae extracts elicited positive (but unspecified) reactions in "many individuals who knew that swimming caused hay fever" at dilutions up to 1:100,000	[53]
1946	Late summer	Lake Keesus, WI, USA	Same subject	N/S		Swimming	As above	N/S	N/S	N/S				[53]
1973-4	Summer	Belgrano Park pond, Santa Fe City, Argentina	N/S	N/S	N/S	Swimming and bathing	G-I symptoms, dermatitis, otitis, conjunctivitis	Mainly *M. aeruginosa*; bloom contained "up to 60,000 colonies/mL"	N/S	N/S	N/S	N/S		[159]
1979	Late summer	Arrowhead Lake, PA, USA	Initial reports: 20-30 children, several adults. 12 children + I adult investigated	N/S	4-12, + adult	Swimming	Headache: 8/13 stomach cramps: 9/13 nausea: 5/13 vomiting: 7/13 diarrhoea: 11/13 fever: 5/13 rash: 1/13 sore or inflamed throat: 3/13	N/S	During exposure, to maximum 12 hours after exposure. Rash on arms & legs of adult ♀ developed "shortly after wading along lake edge"	Most symptoms: <72 hours All symptoms: ≤5 days	Stool samples of four children negative for *Salmonella* and *Shigella*. Throat swab of one child with sore throat negative for viral involvement	N/S	Routine weekly monitoring for faecal coliforms showed counts were ≤40/100mL prior to incident	[64]
1980	Mid-summer	Pocono Highlands Lake, PA, USA	N/S "swimmers"	N/S	N/S	Swimming	Eye irritation, earache, sore throat	*Anabaena* sp.	N/S	N/S	Water samples produced signs of poisoning in mice suggestive of hepatotoxin. LD_{50} = 90 mg/kg (i.p. mouse)	N/S		[56]
1980	Late summer	Lake Lahonton, NV, USA	N/S "several… affected "	N/S	N/S	Water skiing, swimming	Erythema, eye irritation, dizziness, nausea, stomach cramps, diarrhea	*Aphanizomenon flos-aquae*	N/S	N/S	LD_{50} = 500 mg/kg body weight (i.p. mouse)	N/S		[56]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Mixed symptoms														
1980	Mid-summer	Camp William Penn, PA, USA	75-100	N/S	N/S	N/S ("campers affected from contact with water")	Conjunctivitis, sore-red throat, headaches, diarrhoea, nausea	*Anabaena* sp.	N/S	N/S		N/S		[56]
1981	Mid-summer	Harveys Lake, PA, USA	N/S ("many reports…")	N/S	N/S	N/S	Skin irritation, nausea, dizziness, diarrhoea	*Anabaena flos-aquae*	N/S	N/S	Mouse toxicity testing of water showed both neurotoxins and hepatotoxins present. LD_{50} = 125 mg/kg	N/S	Lake closed to public access until early spring	[56]
1989	Early autumn	Rutland Water, Leics, UK, and other UK lakes	N/S ("several")	N/S	N/S	Sail-boarding #	Skin rashes, nausea, vomiting, blistering inside mouth, severe thirst	*M. aeruginosa*	N/S	N/S	Microcystin-LR found to be principal cyanobacterial toxin present	N/S	20 sheep and 15 dogs died over approx 3 weeks in late summer – early spring after contact with bloom scum	[6, 61, 155]
1990	Spring	Lake Cargelligo, NSW, Australia	2 or 3	N/S	N/S	Swimming	Two cases of conjunctivitis, one case of rash	*Anabaena circinalis*	N/S	N/S		N/S	Lake closed as water supply for one month while bloom evident	[62]
1991	Summer-Autumn	Lakes Alexandrina and Albert, SA, Australia	1	N/S	N/S (adult)	Crayfishing	Skin and/or eye symptoms (pruritus, skin rash, sore red eyes)	*Nodularia* sp	N/S	N/S	Case identified retrospectively by either interview with local residents, local health workers or surveillance through local GPs	N/S	7 other cases identified, all with skin and/or eye symptoms. Two of them also had asthma symptoms, one had hay fever symptoms, another a sore throat. Water contact was by showering or bathing	[160]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Mixed symptoms														
1991	Late spring – early summer	Darling River, Wilcannia, NSW, Australia	1	Sole report after surveillance requests to report confirmed or suspected cyanobacteria -related illness during an extensive riverine bloom	N/S (adult)	Water skiing	Skin rash, conjunctivitis, diarrhoea, respiratory difficulty	*Anabaena* spp	N/S	N/S		N/S	All schools along the river system were asked to report increases in illness-related absenteeism, especially for G-I symptoms. No such increase was reported	[152]
1991-2	Summer	River Murray, SA, Australia	11	N/S	1-64	"water sport…. particularly skiing". One of these cases had skin contact through both water sport and residential water use	Contact exposure (n=2): rash, itching, mouth blistering, eye irritation; oral ingestion (n=3): diarrhoea, vomiting, nausea, muscle weakness, sore throat, respiratory difficulty, headache; contact + oral exposure (n=6): mixture of above symptoms	Predominantly *A. circinalis*	N/S	N/S	Cases investigated following telephone or personal complaints to health authorities and water supply management	N/S	15 further cases with exposure to River Murray water from reticulated water supply	[161]
1994	N/S	Lake Velencei, Hungary	100-150	N/S	children at a youth camp	N/S	skin and eye irritation	"heavy bloom" of *M. aeruginosa*	N/S	N/S	N/S	N/S		[162]
1996	N/S	Hollingworth Lake, UK	11	N/S	N/S (sea cadets)	Canoe capsizing trials *	Facial rashes, asthmatic signs, dry sporadic cough, vomiting	*Planktothrix agardhii,* containing three microcystins	Day of, and after exposure	N/S		N/S		[23]
1997	Autumn	Lake Sammamish, WA, USA	N/S ("several")	N/S	"young children"	Swimming	G-I complaints, rashes	*M. aeruginosa,* microcystins measured at approx. 500 µg/g dry weight	N/S	N/S	N/S	N/S	A dog began "heaving and coughing", died four hours after exposure to bloom	[43, 44]

Year	Season	Location	Number affected	Estimates of number unaffected	Age	Water activity	Signs & symptoms	Dominant plankton	Time of onset after exposure	Symptom duration	Diagnostic criteria	Predisposing conditions	Notes	References
Mixed symptoms														
2003	N/S	Lake Iso-Kukkanen, Finland	1	N/S	2 yo child	Swimming	Fever and eye irritation	*A. lemmermannii* sole or dominant cyanobacterium. Saxitoxin measured at 13-270 µg/L (depending on methods). Low levels of microcystins found. Anatoxin-a and degradation products reported	N/S	N/S		N/S		[153]

– cyanobacteria-affected water reportedly ingested (table column: “Water activity”)

* – occupational exposure (table column: “Water activity”)

N/S – not stated

Table 3. Summary of epidemiological studies investigating recreational exposure to cyanobacteria

Country; year study conducted; study author/s; reference	Study design	Study size (*n*)	Main outcomes reported	Proportion of exposed subjects from which statistically significant findings were drawn (%)	Odds ratio (95% confidence interval)
UK, 1990 Philipp [82]	Analytical cross-sectional	246	No statistically significant findings		
UK, 1990 Philipp & Bates [83]	Analytical cross-sectional	363	No statistically significant findings		
UK, 1990 Philipp *et al* [84]	Analytical cross-sectional	246	No statistically significant findings		
Australia, 1992 El Saadi *et al* [85]	Case-control	Approx. 48 (subjects reporting recreational exposure)	No statistically significant findings		
Australia, 1995 Pilotto *et al* [86]	Prospective cohort	852	Increased symptoms at seven days following exposure amongst subjects exposed to more than 5,000 cyanobacterial cells/mL for more than one hour compared to non-bathers	10.9	3.44 (1.09, 10.82)
Australia & USA, 1999 - 2002 Stewart *et al* [87]	Prospective cohort	1,331	Increased reporting at three days following exposure of mild respiratory and pooled symptoms amongst those exposed to cyanobacteria levels exceeding 12mm^2/mL compared to subjects exposed to less than 2.4mm^2/mL	11.2	1.7 (1.0, 2.8) (any symptom) 2.1 (1.1, 4.0) (respiratory symptoms)